

**REMARKS**

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 40-58 are pending in the application. Claim 42 has been withdrawn from consideration pursuant to restriction requirement. Claims 40, 41, and 43-58 are under consideration and stand rejected.

By the present amendment, Claim 45 is canceled without prejudice or disclaimer of the subject matter described therein.

By the present amendment, Claims 40, 42, 43, 44, 48, 51, 58 are amended.

Claim 40 is amended to better describe the claimed subject matter. Support for the amendments to Claim 40 can be found in the specification and claims as originally filed, for example at least at page 6, lines 33-35, and at page 10, line 20.

Claims 42 and 43 have been amended for consistency with the amendment to Claim 40. Claim 44 has been amended to delete an optional clause, which is now recited in new Claim 59.

Claim 48 has been amended to better describe the claimed subject matter and to delete a redundant recitation. Support for the amendments to Claim 48 can be found in the specification and claims as originally filed, for example at least at page 10, lines 4-20.

Claims 51 and 58 have been amended to replace the expression "a promoter which is specifically active in tumor cells" with the more concise "tumor-specific promoter" and to delete the phrase "a promoter which is specifically active in infected cells."

Claim 59 is added to recite subject matter that was canceled from Claim 44.

Claim 60 is added. New Claim 60 describes an embodiment of the invention in which the antibody is modified by fusion to a toxic substance and an immunopotentiating substance. Descriptions of the subject matter of new Claim 60 can be found throughout the Specification and Claims as originally filed. For example, at page 13, lines 21-36, an exemplary embodiment wherein the sequence encoding the antibody is fused to a sequence encoding domains of the CD4, an immunopotentiating substance, and human angiogenin, a toxic substance is described.

No new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of this Amendment.

## **Formal Matters**

### Priority

It has been asserted that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date, with particular reference to 37 C.F.R. § 1.78(a)(2) and (a)(5). In particular, it is asserted that the amendment filed on 12/10/01

changed the nature of the application from a continuation application to a divisional application.

Applicants believe that the all conditions for receiving the benefit of an earlier filing date have been complied with. However, in order to more precisely describe the relationship between the present application and the parent application in view of the amendments to the claims, the first sentence of the specification has been amended to replace the word "continuation" with the word "divisional."

#### Information Disclosure Statement

Applicants understand that two documents, Moritz et al. and Rosenfeld et al. were no longer with the parent application, U.S.S.N. 08/809,110. Accordingly, Applicants have provided herewith copies of these documents for the Examiner's consideration.

Further, Applicants understand that document FR 2706486, which is not in the English language, has not been considered because the Examiner asserts that the Information Disclosure Statement filed 8/13/01 does not contain an explanation of the relevance of this document.

FR 2706486 may be relevant to the present application because it was considered relevant to the parent international application by the International Search Authority. It was cited in the International Search Report in the parent application, which includes a concise statement regarding the relevance of the document. A copy of the International Search Report was among the application papers of the parent file that were submitted

concurrently with the present Application and the information disclosure statement on 08/13/01.

A new form PTO-1449 listing these documents is submitted herewith for the convenience of the Examiner. It is believed that no fees are due under 37 C.F.R. § 1.97(c)(2). However, if it is found that any fees are required, the Commissioner is authorized to charge such fees to the deposit account as described on the accompanying transmittal sheet.

#### Inventorship

It has been asserted that the request to correct the inventorship in the present application is deficient in allegedly lacking: 1) a statement under 37 C.F.R. § 3.73(b); and, in the absence of evidence that inventor Pierre Leroy assigned his interest to Transgene S.A., 2) the consent of Pierre LeRoy.

A statement under 37 C.F.R. § 3.73(b) was submitted with the request to correct inventorship in the present application as shown by the attached stamped return postcard and complete copy of the papers filed on June 10, 2002. On the statement under 37 C.F.R. § 3.73(b) it is noted that the assignment by Pierre Leroy of his interest in the parent application, and thereby also the present application, was recorded at Reel 8533, Frame 0703. Thus, the consent of assignee Transgene S.A. was properly given. Applicants therefore request that the request for correction of the inventorship that was submitted on June 10, 2002 be granted.

Title

It has been asserted that the title is not descriptive. The Examiner has suggested a title directed to the elected species. Applicants continue to assert that the generic linking claims in the present application are patentable at least for the reasons presented herein. Moreover, the restriction requirement has been traversed and Applicants reserve the right to petition from the requirement for restriction under 37 C.F.R. § 1.144.

Applicants believe that an amendment to the title would be premature prior to a resolution of these issues. It is therefore requested that this objection be held in abeyance until such time as the application is found to be allowable and the matter of the restriction requirement is settled.

Claim Objections

Claims 40, 41, 43-48 and 51-58 are objected to as embracing non-elected species. Applicants continue to assert that the generic linking claims of the present application are patentable for at least the reasons presented herein. Moreover, the restriction requirement has been traversed and Applicants reserve the right to petition from the requirement for restriction under 37 C.F.R. § 1.144. Applicants believe that an amendment to these claims reflecting the election of species would be premature prior to a resolution of these issues. It is therefore requested that this objection be held in abeyance until such time as

the application is found to be allowable and the matter of the restriction requirement is settled.

Claim 44 is objected to for the recitation of the parenthetical pluralization in "protein(s)." Claim 44 has now been amended to recite the more formal "protein or proteins." Withdrawal of the objection is requested.

**Rejections under 35 U.S.C. § 112, first paragraph**

Claim 48 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, it is asserted that Claim 48 does not indicate that the 2F5 antibody would be modified by an immunopotentiating substance.

Claim 48 depends from Claim 46, which depends from Claim 40. As such, Claim 48 includes all of the descriptive terms of Claims 46 and 40. By the present amendment, Claim 48 has been amended to more clearly describe the claimed invention and to better indicate the antecedent basis of elements recited therein. The Examiner's attention is directed to the Specification, for example at page 10, lines 4-20, where it is pointed out that the toxic or immunopotentiating substance can be fused in frame at the 5' or 3' end of a nucleotide sequence encoding all or part of an antibody. Characteristics of antibodies

and appropriate parts of antibodies are described for example on page 5 of the Specification. Withdrawal of this rejection of Claim 48 is respectfully requested.

Claims 40, 41, 43-47, and 50-58 stand rejected under 35 U.S.C. § 112, first paragraph because the specification is allegedly not enabling of the full scope of these claims. Specifically, while acknowledging that the Specification is enabling for the use of human adenoviruses, it is asserted that the Specification is not enabling for all non-human adenoviruses. Without acceding to the rejection, but simply in order to expedite prosecution of the present application, Claims 40 and 44 have been amended to recite that the claimed recombinant adenoviral vectors have been derived from a human adenovirus. In view of these amendments, Claim 45 has been canceled without prejudice or disclaimer. Thus, Claims 40, 41, 43-47 and 50-58, as amended, are enabled as acknowledged in the Official Action. Withdrawal of this rejection of Claims 40, 41, 43-47, and 50-58 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 48 and 48 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Specifically, the Examiner has asserted that either the 2F5 hybridoma cell lines or the plasmids pTG2676 and pTG2677 are required.

Applicants point out that the 2F5 hybridomas are well known, have been extensively studied, are described in the patent literature, and have been deposited by their creators in EACC (Porton Down, Salisbury, Great Britain) on September 17, 1990 under

the accession number 90091704 as described in U.S. Patent No. 5,831,034 (Exhibit A) at col. 10, lines 18-21, U.S. Patent No. 6,268,484 (Exhibit B) at col. 6, lines 24-25, and other patent literature.

That the material is known and available is also shown by patents awarded to others, for example, Pai et al. (U.S. Patent No. 6,482,928; Exhibit C) which discloses a crystalline form of part of the 2F5 antibody. As shown by Pai et al., the source of the 2F5 antibody is so well known and available that the U.S. Patent and Trademark Office has held that the patent is enabled without even a mention of the source for the starting material, let alone a new and separate deposit. Pai et al. also demonstrates that the amino acid sequence of the heavy and light chains of 2F5 is known. It is within the skill of the ordinary practitioner to construct a nucleic acid sequence that encodes these sequences using a combination of synthesis and PCR.

In view of the foregoing, it is apparent that material necessary to make and use the invention is both known and available. Accordingly, withdrawal of the rejection of Claims 48 and 49 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

**Rejections under 35 U.S.C. § 112, second paragraph**

Claims 40, 41, 43-48 and 51-58 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, it is asserted that the scope of immunopotentiating substance is unclear and that the nature of the modification described by the claims is unclear.

With regard to immunopotentiating substances, these are clearly defined in the specification as a protein capable of enhancing the host's immune response to the target antigen to which the modified antibody is directed. See, for example, page 7, lines 33-39 and page 8, lines 22-38.

With regard to the nature of the modification, Applicant's believe that one of skill in the art would understand the usage of "modified by" referring to the substance comprising a modification of the antibody. However, simply in order to expedite prosecution, Claims 40, 42, 43 and 48 have been amended to recite "modified by fusion to" thereby making the nature of the modification more clear.

Claim 44 has been rejected for recitation of "such as." Claim 44 has been amended to delete the optional clause, which is now recited in new Claim 59.

It is asserted that the metes and bounds of Claim 48 are unclear. By the present amendment, Claim 48 has been amended to more clearly indicate the antecedent relationship of the exogenous nucleotide sequence.

Claims 51 and 58 have been rejected, because allegedly there is insufficient antecedent basis for "the infected cells" and the meaning of "promoter which is specifically active" is allegedly not defined. Claims 51 and 58 have been amended to eliminate the potentially superfluous "the infected cells" and to replace the phrase "promoter which is specifically active in tumor cells" with "tumor-specific promoter." One of skill in the art understands that a tumor-specific promoter is a promoter that is active in tumor cells to a substantially greater extent than non-tumor cells.

In view of the foregoing, the metes and bounds of the claimed invention will be apparent to one of skill in the art. Accordingly, withdrawal of the rejection of Claims 40, 41, 43-48 and 51-58 under 35 U.S.C. § 112, second paragraph is respectfully requested.

**Rejections under 35 U.S.C. § 102**

Claims 40, 41, 43-47 and 51-58 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kolls et al. (Proc. Natl. Acad. Sci. USA 91:215-219, Jan. 1994). The rejection is respectfully traversed.

First, it is noted that Kolls et al. was published less than one year prior to the priority date of the present application. Therefore, Kolls et al. is not prior art under 35 U.S.C. § 102(b).

Moreover, to the extent that Kolls et al. might be applied to a rejection under another sub-section of 35 U.S.C. § 102, the reference does not anticipate, or even suggest the presently claimed invention. To anticipate a claim, a single reference must disclose all the elements of the claim arranged as in the claim.

Kolls et al. discloses an adenoviral vector expressing part of an antibody fused to the extracellular fragment of the TNF receptor. The TNF receptor fragment is neither a toxic substance or an immunopotentiating substance. TNF is known as an immunopotentiating substance. As described by Kolls et al. the TNF receptor fragment is a TNF inhibitor which produces an effect similar to a knock-out of the TNF receptor. (See, Kolls et al. at page 217.) Thus, the TNF receptor fragment taught by Kolls et al. is a

immunosuppressive substance, which is the opposite of an immunopotentiating substance as recited in the present claims and described in the specification, for example, at page 7, lines 33-39 and page 8, lines 22-38. Thus, Kolls et al. not only fails to anticipate the present invention, Kolls et al. teaches an opposite to the present invention.

For at least the foregoing reasons, Applicant's request the withdrawal of the rejection of Claims 40, 41, 43-47 and 51-58

### **Rejections under 35 U.S.C. § 103**

Claims 40, 41, 43-47 and 51-58 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Allaway et al. ( WO 94/19017) in view of Berkner (WO 90/01550). The rejection is respectfully traversed, because the proposed combination fails to teach or suggest every element of the claimed invention, and there would be no motivation to make the proposed combination.

Allaway et al. is related to the use of the extracellular domain of CD4 (sCD4). The serum half-life of sCD4 is generally very short. Chimeric sCD4 based molecules, such as sCD4 fused to a non-specific immunoglobulin (e.g. mouse IgG), were created to extend the half-life of the sCD4. The chimeric sCD4 is expressed in CHO cells, allowed to form dimers or tetramers and purified. Allaway et al. also describes a composition comprising the sCD4 chimera and a separate antibody. The separate antibody can be the anti-HIV antibody 2F5.

Allaway et al. does not teach or suggest forming a fusion between an antibody directed against a tumor or an epitope specific for an infectious and pathogenic organism and a toxic or immunopotentiating substance as recited in the Claims as amended. Allaway et al. teaches the co-administration of separate antibody and chimeric-sCD4 that is expressed in culture and combined in a pharmaceutical composition. Allaway does not teach or suggest administration of an adenoviral vector which directs the expression of a fusion of an antibody directed against a tumor or an epitope specific for an infectious and pathogenic organism and a toxic or immunopotentiating substance. Berkner et al. does not cure the deficiencies of Allaway et al.

Moreover, there would be no motivation to create anything close to the presently claimed vectors by combination with the teachings Berkner et al. Berkner et al. relates to the use of IRES polycistronic transcription units to achieve expression of proteins occurring as multi-subunit polypeptides. Berkner et al. does not teach or suggest an adenoviral vector which directs the expression of a fusion of an antibody directed against a tumor or an epitope specific for an infectious and pathogenic organism and a toxic or immunopotentiating substance. Even if Berkner et al. provides a general suggestion to use an IRES-containing transcription units in an adenoviral vector, this reference fails to provide a reasonable expectation of success of creating therapeutic quantities of complex multimeric proteins. It should be noted that Berkner et al. only illustrates expression of non-multimeric and non-therapeutic proteins (CAT and DFHR) which can be selected for so as to maintain production. In view of the limited demonstration of functionality in

Berkner et al. and the difficulties inherent in such an undertaking, one of skill in the art would not have a reasonable expectation of combining Allaway et al. and Berkner et al. as proposed.

Thus, the cited references in combination fail to teach or suggest every element of the claimed invention. Moreover, there would be no motivation to combine the teachings of the references, because the teachings of Berkner et al. are insufficient to provide a reasonable expectation of success of expressing the complex multimeric polypeptides of Allaway et al. For at least these reasons, it is apparent that the cited references cannot support a prima facie case of obviousness. Accordingly, withdrawal of the rejection of Claims 40, 41, 43-47 and 51-58 under 35 U.S.C. § 103 is respectfully requested.

#### **Regarding the Species Election**

The Examiner has acknowledged Applicants' election with traverse of Group VII, with a species election of CD4. The Examiner has acknowledged that Claims 40, 41, 44-48 and 51-58 link all the groups set forth in the restriction requirement.

From the foregoing it is clear that the linking claims are allowable over the prior art of record. Accordingly, Applicants respectfully request withdrawal of the restriction requirement and examination of the entire invention as claimed.

The Examiner has asserted that the traversal arguments were non-persuasive and has made the restriction requirement final. However, Applicants believe that the reason's given are erroneous at least as follows:

The wrong standard is applied in determining whether the incrementally greater search burden of examining the invention as claimed warrants the present restriction requirement according to M.P.E.P. § 803. The Examiner asserts that a search for one toxic substance in the context of the invention is not the same as a search for another. Applicants respectfully point out that the standard is not any additional search burden, but rather a serious burden is required. This standard balances the individual burden on the Examiner with the substantial burden on the rest of the Office, the Applicants, and the Public that splitting an application into a multitude of divisional applications imposes. The reasons provided in the Official Action do not establish that there would be a serious burden in view of the common classification of the groups, the generic nature of the claims, and the substantially overlapping subject matter.

Moreover, the inventions of groups I-VI are related in they have the same modes of operation, functions and effects, expression of a molecule capable of targeted delivery of a toxic substance to neutralize a tumor or pathogenic organism. Group VII is related to each of Groups I-VI in these groups recite aspects that are taught as capable as being used together. This is the subject of new Claim 60, which is described, for example, at page 13, lines 21-36, an exemplary embodiment wherein the sequence encoding the antibody is fused to a sequence encoding domains of the CD4, an immunopotentiating substance, and human angiogenin, a toxic substance is described. Group VIII represents this use of features of Group VII with features of an embodiment from one Groups I-VI. For at least these reasons, Applicants respectfully request withdrawal of the finality of the restriction

requirement and withdrawal of the requirement. Applicants reserve the right to petition from the restriction requirement as set forth in 37 C.F.R. § 1.144.

**CONCLUSION**

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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By: \_\_\_\_\_



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